REMARKS

Applicants respectfully request reconsideration of the present application in view of the foregoing amendments and in view of the reasons that follow.

In the specification, the paragraph starting at page 9, line 27, (paragraph **[0052]** of U.S. 2002/0102569), has been amended to delete the row that includes clone 008031_Cf.1.

Claim 34 has been amended. Applicants respectfully contend that support for amended claim 34 is provided at page 9, line 27 to page 10, line 2 (paragraph **[0052]** of U.S. 2002/0102569).

This amendment adds, changes and/or deletes claims in this application. A detailed listing of all claims that are, or were, in the application, irrespective of whether the claim(s) remain under examination in the application, is presented, with an appropriate defined status identifier.

After amending the claims as set forth above, claims 26, 28-31, 33-42 are now pending in this application. Claims 35-39 are withdrawn.

Specification

In the Office Action dated May 4, 2004, the Examiner objected to the specification, stating that "because as amended February 12, 2004 it refers to the percent identity between SEQ ID NO:2 and a clone (specification at page 9-10)" (emphasis added). The Examiner stated that "deletion of the row, for example, is suggested." In response to the objection, Applicants have adopted the Examiner's suggestion and amended the specification to delete the row that includes clone 008031_Cf.1. As such, Applicants request that the Examiner reconsider and withdraw the objection.

Claim Rejections – 35 U.S.C. § 112, first paragraph

In the Office Action, the Examiner rejected claims 40-42 under 35 U.S.C. § 112, first paragraph, "as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time

the application was filed, had possession of the claimed invention." In particular, the Examiner asserted that the specification does not provide support "for any fragment of SEQ ID NO:2 encoding at least 5 amino acids." The Examiner noted that "the specification provides a definition of an oligopeptide as 'an amino acid sequence from about five residues to about 15 residues that [is] used as part of a fusion protein to produce an antibody.'" However, the Examiner contended that "[t]he specification is silent with regard to a polynucleotide encoding said oligopeptide." Applicants respectfully traverse the rejection.

Applicants note that at page 15, line 10, ([paragraph **[0080]** of U.S. 2002/0102569), the specification states:

> **[0080]** Various hosts including, but not limited to, goats, rabbits, rats, mice, and human cell lines ***may be immunized by injection with cancer marker protein or any portion thereof.*** Adjuvants such as Freund's, mineral gels, and surface active substances such as lysolecithin, pluronic polyols, polyanions, peptides, oil emulsions, keyhole limpet hemacyanin (KLH), and dinitrophenol may be used to increase immunological response. ***The oligopeptide, peptide, or portion of protein used to induce antibodies should consist of at least about five amino acids, more preferably ten amino acids, which are identical to a portion of the natural protein.*** Oligopeptides may be fused with proteins such as KLH in order to produce antibodies to the chimeric molecule.

Further, at page 13, lines 7-8, (paragraph **[0070]** of U.S. 2002/0102569), the specification states:

> **[0070]** Any one of a multitude of cDNAs encoding the cancer marker protein may be cloned into a vector and used to express ***the protein, or portions thereof***, in host cells....

As stated in the MPEP § 2163 I.B., "[w]hile there is no *in haec verba* requirement, newly added claim limitations must be supported in the specification through ***express, implicit, or inherent disclosure***. In view of the express, implicit, or inherent disclosure of the specification, Applicants respectfully contend that "one skilled in the art would ***reasonably conclude*** that the inventors had possession of the claimed invention." *See* MPEP § 2163 I.

(emphasis added). Applicants respectfully request that the Examiner reconsider and withdraw the rejection under 35 U.S.C. § 112, first paragraph.

Claim Rejections – 35 U.S.C. § 101

In the Office Action, the Examiner rejected claims 26, 28-31, 33, 34, and 40-42 under 35 U.S.C. § 101, stating that "the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility." Applicants respectfully traverse the rejection for the following reasons.

I. An invention satisfies the utility requirement of 35 U.S.C. § 101 if, based on the totality of the record, it is more likely than not that a person of ordinary skill in the art would consider that the claimed subject matter has at least one specific, substantial, and credible utility.

As stated in the MPEP § 2107, "[i]f the applicants have asserted that the claimed invention is useful for any practical purpose (i.e., it has a "specific and substantial utility") and the assertion would be considered credible by a person of ordinary skill in the art, do not impose a rejection based on lack of utility." MPEP 8th Edition, § 2107 II.(B)(1). In describing the amount and character of evidence necessary to support an asserted utility, the MPEP states:

> There is no predetermined amount or character of evidence that must be provided by an applicant to support an asserted utility, therapeutic or otherwise....Instead, evidence will be sufficient if, considered as a whole, it leads a person of ordinary skill in the art to conclude that the asserted utility is ***more likely than not true***."

See id. at § 2107.01 VII. (***emphasis in original***).

In further describing the utility requirement, the MPEP states:

> However, as the Federal Circuit has stated, "[t]o violate [35 U.S.C.] 101 the claimed device must be ***totally incapable of achieving a useful result***." *Brooktree Corp. v. Advanced Micro Devices, Inc.*, 977 F.2d 1555, 1571, 24 USPQ2d 1401, 1412 (Fed. Cir. 1992) (emphasis added). *See also E.I. du Pont De Nemours and Co. v. Berkley and Co.*, 620 F.2d 1247, 1260 n.17, 205 USPQ 1, 10 n.17 (8th Cir. 1980) ("A small degree of utility is sufficient....The claimed invention must ***only be capable of performing some beneficial function***....An invention does not lack utility merely because the particular embodiment disclosed in the patent lacks perfection or performs crudely....A commercially successful product is not required....Nor is it essential that the invention accomplish all its intended functions...or operate under all conditions...partial success being sufficient to demonstrate patentable utility....In short, the defense of non-utility cannot be sustained without proof of total incapacity."). ***If an invention is only partially successful in achieving a useful result, a rejection of the claimed invention as a whole based on a lack of utility is not appropriate***. *See In re Brana*, 51 F.3d 1560, 34 USPQ2d 1436 (Fed. Cir. 1995)(emphasis added); *In re Gardner*, 475 F.2d 1389, 177 USPQ 396 (CCPA), *reh'g denied*, 480 F.2d 879 (CCPA 1973); *In re Marzocchi*, 439 F.2d 220, 169 USPQ 367 (CCPA 1971).

See id. at § 2107.01 II.

Further, "[w]here the asserted utility is not specific or substantial, a *prima facie* showing must establish that it is ***more likely than not*** that a person of ordinary skill in the art would not consider that ***any utility asserted by the applicants*** would be specific and substantial. *See id.* at § 2107 II.(C)(1). Likewise, "[w]here the asserted specific and substantial utility is not credible, a *prima facie* showing of no specific and substantial credible utility must establish that it is ***more likely than not*** that a person skilled in the art would not consider credible ***any specific and substantial utility*** asserted by the applicants for the claimed invention." *See id.* at § 2107 II.(C)(2).

After an Applicant has rebutted a *prima facie* showing of lack of utility, "[o]nly where the ***totality of the record*** continues to show that the asserted utility is not specific, substantial, and credible should a rejection based on lack of utility be maintained." *See id.* at § 2107 II.(D). As such, based on the ***totality of the record***, Applicants respectfully contend that ***it is more likely than not*** that a person of ordinary skill in the art would consider that the claimed subject matter has at least one specific, substantial, and credible utility.

II. Applicants have disclosed at least one specific, substantial, and credible utility for the claimed subject matter.

Applicants note that the specification describes a protein designated by SEQ ID NO:1. The specification also describes a polynucleotide encoding the protein designated by SEQ ID NO:1 and having a DNA sequence designated by SEQ ID NO:2. Applicants have indicated that the protein is useful as a "cancer marker" and have designated the protein as "cancer marker protein."

Applicants further note that the specification discloses Northern analyses for the cancer marker protein in categories of cDNA libraries from hemic/immune, urinary tract, digestive system, female and male reproductive systems. Only non-normalized libraries were included in the analyses, and all normalized or pooled libraries were excluded from the analyses. In particular, the Northern analyses were used to evaluate expression of the cancer marker protein mRNA in lymphoma and cancers of the bladder, colon, kidney, ovary, and testis. The evaluation involved examination of both ***differential expression in each of the cancers*** and ***lack of expression in control tissue and in tissues associated with other disorders***. The results demonstrate that the cancer marker protein mRNA is differentially expressed in at least lymphoma, metastatic adenocarcinoma of the colon, transitional cell carcinoma of the bladder, metastatic endometrial cancer, and testis tumor.

A. *Transcripts encoding the cancer marker protein are differentially expressed in lymphoma.*

As shown at page 32, lines 24-32 (*i.e.*, at paragraph **[0176]** and accompanying table), expression of the cancer marker protein mRNA was two-fold greater than seen in activated lymphocytes (MLR=mixed lyphocytic reaction) and six-fold greater than seen in PBMC. ***No expression was seen in three other libraries made from activated T-cells or in five other libraries made from untreated or non-activated T-cells.***

B. *Transcripts encoding the cancer marker protein are differentially expressed in metastatic adenocarcinoma of the colon.*

As shown at page 32, line 34 to page 33, line 6, (*i.e.*, at paragraph **[0177]** and accompanying table), expression of the cancer marker protein mRNA was higher in tissue associated with metastatic cancer than in a contained tumor and two-fold greater than seen in epithelium or any other cytologically normal libraries. Of 54 libraries in the analysis, ***the cancer marker protein was not significantly expressed in five libraries with diagnosed Crohn's disease, in seven libraries with diagnosed chronic ulcerative colitis and three libraries with diagnosed polyposis.***

C. *Transcripts encoding the cancer marker protein were differentially expressed in transitional cell carcinoma of the bladder.*

As shown at page 33, lines 19-28, (*i.e.*, at paragraph **[0178]** and accompanying table), expression of the cancer marker protein mRNA was more than two-fold greater than seen in association with chronic cystitis or cytologically normal bladder. Of 17 bladder libraries examined in the analysis, ***no expression was seen in any other cancerous or cytologically normal libraries.***

D. *Transcripts encoding the cancer marker protein were differentially expressed in metastatic endometrial cancer.*

As shown at page 34, line 30 to page 35, line 2, (*i.e.*, at paragraph **[0180]** and accompanying table), expression of the cancer marker protein mRNA in metastatic endometrioid carcinoma was more than two-fold that seen in ovary tissue with identified endometriosis and leiomyomata, leiomyomata, and mucinous cystadenocarcinoma. Of the 34 ovary libraries examined in the analysis, ***expression of the cancer marker protein was not observed or was not significant in ten libraries diagnosed with serous papillary adenocarcinoma, seven libraries diagnosed with leiomyomata, four libraries diagnosed with mucinous cystadenocarcinoma, three libraries diagnosed with dermoid or follicular cysts, or in libraries constructed from cytologically normal tissue.***

E. *Transcripts encoding the cancer marker protein were differentially expressed in testis tumor.*

As shown at page 35, lines 19-26, (*i.e.*, at paragraph **[0181]** and accompanying table), expression of the cancer marker protein mRNA in testis tumor was more than two-fold that seen in a embryonal carcinoma library and a library constructed from testicular tissue removed from a male who died from cirrhosis of the liver. ***No expression was seen in two seminoma libraries and in seven other cytologically normal libraries.***

F. *The protein designated by SEQ ID NO:1 may function as a cancer marker protein for cancer resulting from dematomyositis.*

In addition, the protein designated by SEQ ID NO:1 from amino acids 74-315 is 100% identical to a protein designated "Dermatomyositis ***associated with cancer*** putative autoantigen" from amino acids 302-543. *See* BLAST results, enclosed herewith, and GenBank Accession No. BAB62751, (submitted by Onouchi, H., unpublished), also enclosed herewith. Dermatomyositis is an immune-related connective tissue disease, and ***15 – 30% of patients with dermatomyositis develop cancer***, including lymphatic cancer, colon cancer, bladder cancer, ovarian cancer, and testicular cancer. *See, e.g.*, Wakata, *et al.*, *Polymyositis and dermatomyositis associated with malignancy: a 30-year retrospective study*, INT. J.

DERMATOL., 41:729-34 (2002); Langan *et al.*, *Dermatomyositis associated with angiotropic lymphoma*, CLIN. DERMATOL., 28:597-599 (2003); Gluck *et al.*, *Dermatomyositis, carcinoma of colon and meningioma in the same patient*, J. DERMATOL., 20:719-22 (1993); Apaydin *et al.*, J. EUR. ACAD. DERMATOL. VENEREOL., 16:172-4 (2002); Hagman *et al.*, *Dermatomyositis associated with ovarian transitional carcinoma*, J. AM. ACAD. DERMATOL., 45:642-4 (2001); and Di Stasi, *et al.*, *Dermatomyositis associated with testicular germ cell cancer*, J. UROL., 163:240 (2000). *See also* Zhang *et al.*, *The Dermatomyositis-Specific Autoantigen Mi2 Is a Component of a Complex Containing Histone Deacetylase and Nucleosome Remodeling Activities*, Cell, 95:279-89 (1998). Applicants have enclosed copies of the aforementioned scientific articles for the Examiner's reference.

Dermatomyositis is often characterized by the presence of anti-nuclear auto-antibodies, (*e.g.*, auto-antibodies to the nuclear Mi-2 auto-antigen). *See, e.g.*, Targoff, *Idiopathic inflammatory myopathy: autoantibody update*, CURR. RHEUMATOL. REP., 4:434-41 (2002). The Mi-2 auto-antigen is related to the "metastasis-associated protein 1" and may play a role in cancer associated with dermatomyositis. *See* Zhang *et al.*, *The Dermatomyositis-Specific Autoantigen Mi2 Is a Component of a Complex Containing Histone Deacetylase and Nucleosome Remodeling Activities*, CELL, 95:279-89 (1998), at page 287, (describing "The Connection between Histone Deacetylase, Chromatin Structure, Dermatomyositis, and Cancer").

Further, a portion of the protein designated by SEQ ID NO:1 from amino acids 74-315 is 100% identical to a portion of a nuclear protein domain designated "YTH domain family 1" from amino acids 302-543. *See* BLAST results enclosed herewith; GenBank Accession No. NP_060268 entry enclosed herewith. The YTH domain was identified in a nuclear protein called YT521-B, which has been characterized as a pre-mRNA splicing factor. *See* Stoilov *et al.*, *YTH: a new domain in nuclear proteins*, TRENDS IN BIOCHEM. SCI., Vol. 27, pp. 495-497 (2002). Stoilov *et al.* describe the "YTH domain" as being present in nuclear proteins and predict that the biological function of the YTH domain is to bind to RNA. *See* Stoilov *et al.* at page 497. Notably, auto-antibodies to ribonucleoproteins involved in mRNA splicing (*e.g.*, auto-antibodies to U2 RNP) are present in patients with scleroderma/polymyositis overlap syndrome, which is an immune-related connective tissue disease related to dermatomyositis.

See Targoff *et al.*, *Humoral immunity in polymyositis/dermatomyositis*, J. INVEST. DERMATOL., 100:116S-123S (1993). Therefore, the totality of the record suggests that the protein designated by SEQ ID NO:1 is a nucleoprotein, likely a splicing factor, which functions as an auto-antigen in patients with dermatomyositis, and that auto-antibodies to the protein designated SEQ ID NO:1 may be indicative of the patient's likelihood of developing cancer. *See* Title of Onouchi, H., unpublished, "Dermatomyositis associated with cancer putative autoantigen," referenced in GenBank Accession No. AB055518 deposit information. Applicants have enclosed copies of the aforementioned scientific articles for the Examiner's reference.

Therefore, based on the ***totality of the record***, Applicants respectfully contend that ***it is more likely than not*** that a person of ordinary skill in the art would consider that the claimed subject matter has ***at least one*** specific, substantial, and credible utility. Applicants have shown that the cancer marker protein mRNA is differentially expressed in at least: (A) a cDNA library derived from lymphoma cells relative to cDNA libraries derived from activated or unactivated T-cells; (B) a cDNA library derived from metastatic adenocarcinoma of the colon relative to cDNA libraries derived from contained tumor or cytologically normal cells/tissue; (C) a cDNA library derived from transitional cell carcinoma of the bladder relative to cDNA libraries derived from chronic cystitis or cytologically normal bladder; (D) a cDNA library derived from metastatic endometrial cancer relative to cDNA libraries derived from identified endometriosis and leiomyomata, leiomyomata, and mucinous cystadenocarcinoma; and (E) a cDNA library derived from testis tumor relative to cDNA libraries derived from embryonal carcinoma or testicular tissue removed from a male who died from cirrhosis of the liver. In addition, others have identified proteins/domains that are at least partially identical to the protein designated by SEQ ID NO:1. These include proteins/domains designated "Dermatomyositis associated with cancer putative autoantigen" and "YTH domain family 1," which suggest that the presence of auto-antibodies to the protein designated by SEQ ID NO:1 in patients with dermatomyositis are an indication of whether the patient will develop cancer.

As noted above, to satisfy the utility requirement of 35 U.S.C. § 101, "the claimed invention must ***only be capable of performing some beneficial function***." *See* MPEP § 2107.01 II. (emphasis added) (citing *E.I. du Pont De Nemours and Co. v. Berkley and Co.*, 620 F.2d 1247, 1260 n.17, 205 USPQ 1, 10 n.17 (8th Cir. 1980)). Nevertheless, Applicants have described ***several specific, substantial, and credible utilities*** for the claimed subject matter. Applicants respectfully contend that, based on the totality of the record, it is more likely than not that a person of ordinary skill in the art would consider that ***at least one of the utilities asserted by the Applicants*** is specific, substantial, and credible. Therefore, Applicants respectfully request that the Examiner reconsider and withdraw the rejection under 35 U.S.C. § 101.

Claim Rejections – 35 U.S.C. § 112

In the Office Action, the Examiner also rejected claims 26, 28-31, 33, 34, and 40-42 under 35 U.S.C. § 112, first paragraph, stating that "since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention." For the reasons stated above in response to the rejection under 35 U.S.C. § 101, Applicants respectfully traverse the rejection under 35 U.S.C. § 112, first paragraph.

Claim Rejections – 35 U.S.C. § 102

In the Office Action, the Examiner rejected claim 34 under 35 U.S.C. § 102(a) as being anticipated by Hillier *et al.* Applicants have amended claim 34 to recite "having about 90% identity to a sequence of SEQ ID NO:2 from nucleotide 667 to nucleotide 1173." As such, Hillier *et al.* do not anticipate amended claim 34, and Applicants respectfully request that the Examiner reconsider and withdraw the rejection under 35 U.S.C. § 102(a).

Applicants believe that the present application is now in condition for allowance. Favorable reconsideration of the application as amended is respectfully requested.

The Examiner is invited to contact the undersigned by telephone if it is felt that a telephone interview would advance the prosecution of the present application.

Respectfully submitted,

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